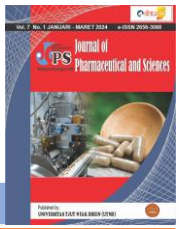
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Dose Optimization of Sacubitril/Valsartan and Its Impact on Clinical Outcomes in Heart Failure with Reduced Ejection Fraction: A Systematic Review

Optimalisasi Dosis Sacubitril/Valsartan dan Dampaknya terhadap Luaran Klinis pada Gagal Jantung dengan Fraksi Ejeksi Rendah: Sebuah Tinjauan Sistematis

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Abstract

Heart failure with reduced ejection fraction (HFrEF) remains a major cause of mortality and hospitalizations. While sacubitril/valsartan is essential, real-world dosing often falls below guideline recommendations. This systematic review evaluated the association between sacubitril/valsartan dose categories and clinical prognosis across seven observational studies (N=7,814). Research findings indicate that variations in sacubitril/valsartan dosage are associated with differences in clinical outcomes, influenced by tolerability and treatment preferences. High-dose therapy (400 mg daily) was associated with a 75% lower all-cause mortality and 77% lower cardiovascular mortality compared with low doses. Conversely, the lowest dose (24/26 mg twice daily) exhibited a 2.56-fold higher mortality risk versus target doses. Reaching ≥50% of the target dose was associated with a 70% lower mortality risk in patients aged <65 years (HR 0.30) and 49% in those aged 65–74 years (HR 0.51). Target doses were also associated with a 66% lower rate of composite death and hospitalization across hemodynamic profiles. Initiating therapy at a very low dose (25 mg twice daily) in high-risk patients appeared well-tolerated, yielding outcomes comparable to standard initiation. Real-world evidence demonstrates that higher sacubitril/valsartan doses are consistently associated with improved survival and reduced hospitalization rates, underscoring the importance of individualized dose optimization.

***Keywords*: sacubitril/valsartan; HFrEF; hospitalization; rehospitalization; mortality**

Abstrak

Gagal jantung dengan fraksi ejeksi yang menurun (HFrEF) tetap menjadi penyebab utama kematian dan rawat inap. Meskipun penggunaan sacubitril/valsartan sangat penting, dosis yang diterapkan dalam praktik klinis nyata sering kali berada di bawah rekomendasi pedoman. Tinjauan sistematis ini mengevaluasi hubungan antara kategori dosis sacubitril/valsartan dan prognosis klinis berdasarkan tujuh studi observasional (N=7.814). Hasil penelitian menunjukkan bahwa variasi dosis sacubitril/valsartan berkaitan dengan perbedaan luaran klinis yang dipengaruhi oleh tolerabilitas dan keinginan terapi. Terapi dosis tinggi (400 mg per hari) dikaitkan dengan penurunan risiko kematian akibat semua penyebab sebesar 75% dan penurunan risiko kematian akibat penyakit kardiovaskular sebesar 77% dibandingkan dengan dosis rendah. Sebaliknya, dosis terendah (24/26 mg dua kali sehari) menunjukkan risiko kematian 2,56 kali lebih tinggi dibandingkan dengan dosis target. Pencapaian dosis ≥50% dari dosis target dikaitkan dengan penurunan risiko kematian sebesar 70% pada pasien berusia <65 tahun (HR 0,30) dan sebesar 49% pada pasien berusia 65–74 tahun (HR 0,51). Dosis target juga dikaitkan dengan penurunan tingkat gabungan kematian dan rawat inap sebesar 66% pada berbagai profil hemodinamik. Memulai terapi dengan dosis sangat rendah (25 mg dua kali sehari) pada pasien berisiko tinggi terbukti dapat ditoleransi dengan baik dan menghasilkan luaran yang sebanding dengan inisiasi standar. Bukti dari praktik klinis nyata menunjukkan bahwa dosis sacubitril/valsartan yang lebih tinggi secara konsisten dikaitkan dengan peningkatan kelangsungan hidup dan penurunan angka rawat inap, yang menegaskan pentingnya optimalisasi dosis yang disesuaikan secara individual.

***Kata Kunci*: sacubitril/valsartan; HFrEF; rawat inap; rawat inap ulang; mortalitas**

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Introduction

The number of individuals experiencing heart failure is reaches 64 millions across the globe, and this figure continues to rise [1]. The rate of heart failure-related rehospitalization decreased from 1.0 to 0.9 per 1,000 adults between 2010 and 2014 but rose to 1.1 in 2017; this suggests that rehospitalization remains an ongoing burden for patients with cardiac insufficiency [2]. The Swedish Heart Failure Registry (SwedeHF) reports data showing that among 73,769 registered heart failure patients, the HFrEF subtype predominates, accounting for 53% of the total population [3]. Sacubitril/valsartan is a drug from the class of angiotensin receptor neprilysin inhibitor (ARNI) that has been recommended as a primary therapy for HFrEF because, compared with ACE inhibitors, it results in lower rates of hospitalization events related to heart failure and death due to cardiovascular causes among eligible patients [4,5]. In the PARADIGM-HF study, sacubitril/valsartan was shown to be significantly superior to enalapril, reducing the risk of the primary composite outcome (cardiovascular death or hospitalization for heart failure) by 20% (HR 0.80; $p < 0.001$). This risk reduction was driven by balanced, independent reductions in cardiovascular death of 20% (HR 0.80) and in the risk of hospitalization for heart failure of 21% (HR 0.79) [6].

In the progression of heart failure, sacubitril/valsartan has a mechanism of action involving two primary targets. The drug modulates the RAAS while simultaneously optimizing natriuretic peptide system (NPS) activity. Valsartan inhibits AT1 receptor-mediated angiotensin II activity, thereby modulating vasodilation, sodium retention, aldosterone secretion, sympathetic stimulation, and cardiovascular remodeling, which collectively reduce the workload on the heart [7]. The initial dose of sacubitril/valsartan for the treatment of heart failure is usually low and gradually increased according to patient tolerability to reach the target dose. Clinical guidelines recommend achieving the target dose whenever possible, and if full dose adjustment is not possible, the highest tolerated dose should be maintained [4,5]. The findings obtained from the post hoc data analysis of PARADIGM-HF indicate that, patients receiving sacubitril/valsartan or enalapril who required a dose reduction were up to 2.5 times more likely to experience a higher risk of cardiovascular outcomes compared to the group that did not require a dose reduction. Nevertheless, the therapeutic benefits of sacubitril/valsartan are maintained even with dose reduction [8]. Dose uptitration may be constrained by adverse effects including systolic blood pressure, which dropped to bellow 100 mmHg, increase in serum creatinine level to more than 2.5 mg/dL, hyperkalemia (>5.5 mmol/L), and angioedema; The dose is increased gradually until the target dose of 97/103 mg is reached per dose twice daily, If the lower dose is well tolerated [4,9].

In a cross-sectional study of 1,065 cases of hospitalization due to heart failure at a single healthcare center, after propensity score matching, ARNI use in HFrEF patients showed a similar rehospitalization rate to RAAS inhibitor therapy (12 vs. 13 patients), with a comparable time to first rehospitalization (114.5 vs. 126 days) [10]. Furthermore, in 7,893 patients who had undergone propensity score matching, treatment with sacubitril/valsartanshows rates of heart failure-related readmission similar to those of ACEI/ARB (95% CI 0,96–1,19; HR 1,07; p=0,26). Additionally, within a group of Black/African American diagnosed with HFrEF, analysis showed that the composite outcome of death and hospitalization did not differ significantly between the ARNI and ACEI/ARB groups, with a relatively comparable risk between the two groups (HR 1.00; 95% CI 0.88–1.15) [11]. In the ≥75-year-old age group, the benefit of ARNI on hospitalization was also not significant (IRR 1.05; p=0.565) [12]. Furthermore, a Swedish propensity score-matching cohort study show the risk of all-cause hospitalization did not differ significantly (RR 1.02; p=0.76) or cardiovascular hospitalization (RR 1.01; p=0.84) between between patients using ARNI and ACEI/ARB [13]. Previous evidence syntheses have

provided valuable insights into dose optimization in heart failure but have primarily focused on ACE inhibitor dosing or summarized sacubitril/valsartan dosing evidence narratively [14–16].

In Asia, patients with HFrEF have a higher mortality rate compared to patients with HFpEF, at 10.6% and 5.4%, respectively, over a one-year period. Patients from Southeast Asia exhibited significantly higher one-year mortality compared to the South Asian and Northeast Asian groups, at 13.0%, 7.5%, and 7.4%, respectively (P<0.001) [17]. Compared to ACE inhibitors (ACEIs), ARNI therapy lowered the likelihood of a composite endpoint of hospitalization for heart failure or cardiovascular death (26.5% vs 21.8%; HR 0.80), as well as overall mortality (HR 0.84), heart-related mortality (HR 0.80). These findings demonstrate the benefit of ARNI over ACEI in reducing the risk of death in patients with HFrEF [6]. This systematic review was conducted to complement the existing evidence by systematically synthesizing and critically appraising real-world studies evaluating sacubitril/valsartan dose classification, the relationship between different dose categories and clinical outcomes, including heart failure hospitalization, rehospitalization, and mortality, as well as the effect of dose titration and target dose attainment in a population with HFrEF.

Methods

Article Selection and Data Extraction

A total of 431 articles were identified through the initial literature search. Following screening and the removal of duplicates, the number of articles eligible for further processing was reduced to 399. The subsequent stage involved screening titles and abstracts to assess their alignment with the research question. Articles meeting the relevance criteria then underwent full-text review. A total of 238 articles were evaluated against the established inclusion and exclusion criteria. Based on the selection results, seven studies were ultimately included in this systematic review. All stages of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The sequence of article selection stages in this study is illustrated in the PRISMA flow diagram presented in Figure 1.

Eligibility Criteria and Outcome of Interest

Studies will be included if they meet the following criteria: (1) Cohort or registry-based studies involving patients with HFrEF with LVEF ≤40% (or as defined by the original study) aged ≥18 years; (2) studies reporting hospitalization-related outcomes, including heart failure (HF) hospitalization, HF rehospitalization, all-cause rehospitalization, or composite outcomes incorporating HF hospitalization, with a minimum follow-up of 30 days; and (3) Studies were eligible regardless of whether a direct statistical comparison between dose groups was explicitly performed, as long as outcomes could be extracted or interpreted according to dose categories.

We excluded publications that do not present primary research data, such as review articles, editorials, letters, and case reports; studies involving HFpEF or HFmrEF without separate analyses of HFrEF; mixed populations without subgroup analyses; and studies that did not report hospitalization related outcomes. The outcome of interest was heart failure hospitalization and rehospitalization. Both outcomes were compared across different sacubitril/valsartan dose categories. In addition to the primary outcome related to hospitalization, supplementary clinical outcomes such as mortality were also evaluated where available, aiming to provide a broader perspective on the clinical implications of achieving therapeutic doses. Inclusion criteria also required a minimum follow-up period of 30 days.

Search Strategy

The process of gathering scientific articles relevant to this review relied on in-depth searches across three major electronic databases including PubMed, Scopus, and ScienceDirect. The search strategy was formulated using a combination of Boolean operators (AND, OR, and NOT) to enhance the precision of search results. Keywords included standard indexing terms, such as Medical Subject Headings (MeSH), as well as free-text terms such as "sacubitril/valsartan," "ARNI," "heart failure with reduced ejection fraction," "HFrEF," "target dose," "dose titration," "dose dependence," "rehospitalization," and "hospitalization." Given that each database employs distinct indexing systems and search features, the search strategy and syntax were tailored to the specific characteristics of each platform. The search strategy was limited to studies published in English or Indonesian during the period 2016–2026. Full details of the search strategy are presented in Table 1.

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Table 1. Search Strategy database

Database	Search Terms	Filters
PubMed	("Heart Failure with Reduced Ejection Fraction" OR HFrEF OR "Heart Failure") AND ("Sacubitril/Valsartan" OR "Sacubitril-Valsartan" OR ARNI) AND ("Target Dose" OR "Dose Titration" OR "Dose Dependence" OR Uptitration) AND (Hospitalization OR Rehospitalization OR Readmission)	English and Indonesian; 2016–2026
Scopus	("Heart Failure with Reduced Ejection Fraction" OR HFrEF) AND ("Sacubitril/Valsartan" OR ARNI) AND ("Target Dose" OR "Dose Dependence" OR Uptitration) AND (Hospitalization OR Rehospitalization OR Readmission)	
ScienceDirect	("Heart Failure with Reduced Ejection Fraction" OR HFrEF) AND "Sacubitril/Valsartan" AND ("Target Dose" OR "Dose Titration" OR "Dose Escalation") AND (Hospitalization OR Rehospitalization)	

Screening and Selection Process

References obtained from PubMed, Scopus, and ScienceDirect were exported to Zotero to facilitate citation management and the deduplication process. The screening process was carried out by the first author (ASP), while eligible studies were reviewed by a co-author to verify the consistent application of selection criteria. In the event of discrepancies in assessment results, the final decision is reached through discussion until a consensus is achieved. All reasons for exclusion at the full-text review stage are systematically documented and subsequently reported in the PRISMA 2020 flow diagram.

Data Synthesis

Meta-analysis was not performed because dose categories were defined differently across studies, including tablet-strength classifications, daily dose thresholds, achieved dose levels, and target-dose attainment measures. Consequently, effect estimates were not directly comparable across studies. Considerable variability was also observed in outcome definitions, with studies reporting HF hospitalization, HF rehospitalization, all-cause mortality, cardiovascular mortality, or composite endpoints, limiting the feasibility of quantitative pooling. The included studies reported different effect measures (hazard ratios, odds ratios, risk ratios, and incidence rate ratios), further complicating quantitative synthesis. Differences in study design, follow-up duration, and patient characteristics contributed additional clinical and methodological heterogeneity. Due to substantial heterogeneity in dose classification, outcome definitions, effect measures, and study designs, a quantitative meta-analysis was considered inappropriate.

Quality Assessment

The assessment of methodological quality and risk of bias for all included studies was conducted using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies developed by the National Heart, Lung, and Blood Institute (NHLBI). The instrument consists of 14 assessment domains used to evaluate the quality of the included studies. The components evaluated include the clarity of research objectives, characteristics of the included population, participant selection methods, assessment of exposures and outcomes, adequacy of the follow-up period, and control for confounding factors that could potentially influence the study results. Each criterion is evaluated using five rating options in accordance with NHLBI guidelines: "Yes," "No," "Cannot Determine (CD)," "Not Reported (NR)," and "Not Applicable (NA)".

Study quality is determined based on the potential for bias in the evaluated components, without the use of numerical scores. In accordance with NHLBI guidelines, each study is classified as Good, Fair, or Poor based on its methodological quality and potential for bias. The first author independently evaluated the quality of the studies. Subsequently, the assessment results were reviewed with the co-author to ensure that the evaluation process was conducted consistently. An assessment of methodological quality was applied to all studies meeting the eligibility criteria, using 14 assessment domains. Details of the evaluation results are presented in Table 2.

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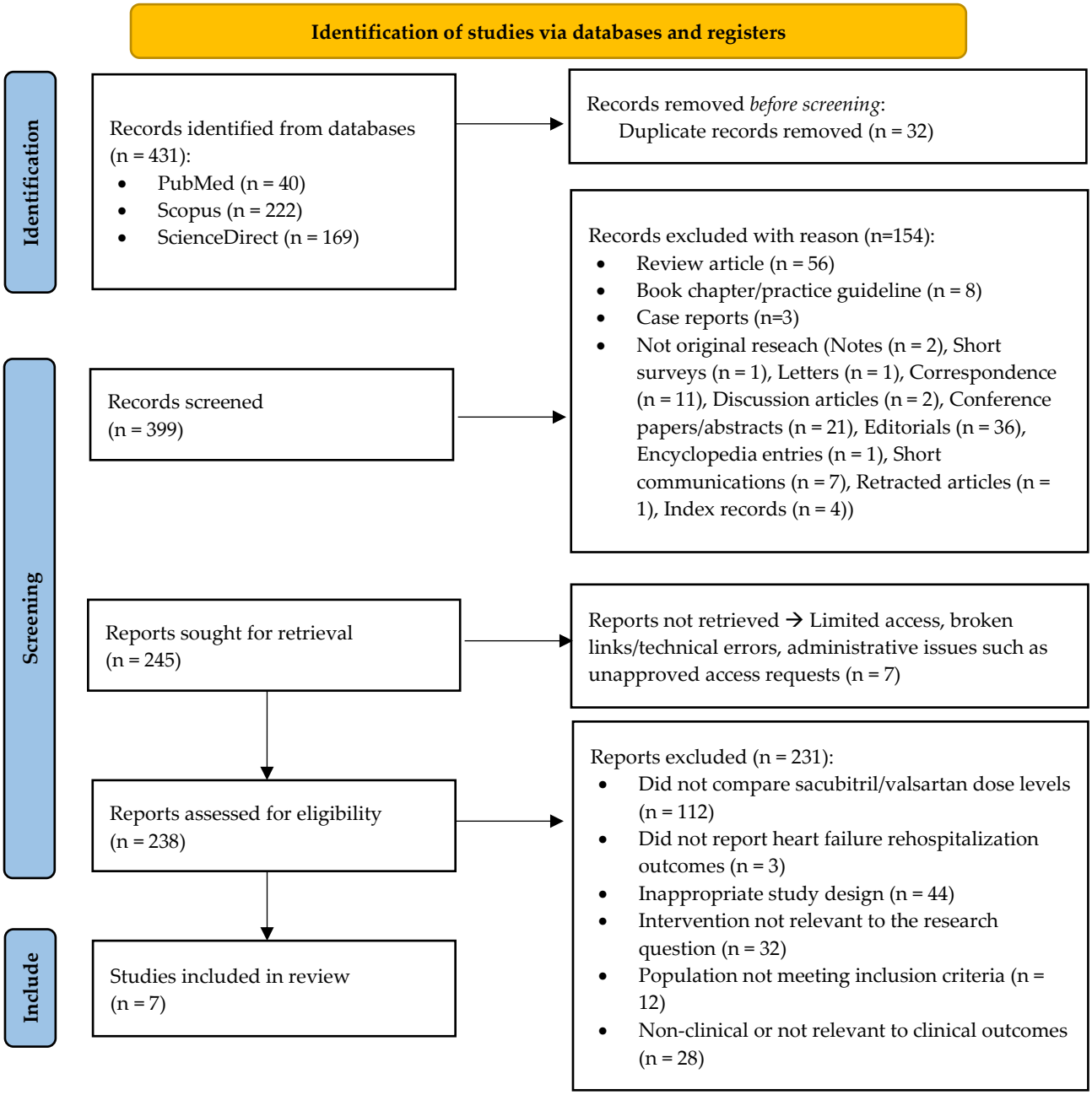


Figure 1: PRISMA flow diagram for study selection

Results and Discussion

Quality Assessment of Included Studies

This systematic review includes seven studies with a total of 7,814 participants deemed relevant to the research objective. Methodological quality assessment of all studies meeting the inclusion criteria was conducted using the NIH Quality Assessment Tool for Cohort Studies. A summary of the evaluation results regarding 14 methodological aspects is presented in Table 2. Quality ratings are grouped as follows: scores of 0–4 indicate poor quality, 5–10 indicate fair quality, and 11–14 indicate good quality [18]. No studies were rated as "poor." In the table, the code “Y” indicates that a criterion was met, “No” indicates the criterion was not met, “NR” indicates the necessary information was not reported, “CD” indicates that the assessment could not be determined, and “NA” is used for criteria not applicable to the study being assessed. Based on the overall assessment results, five studies fell into the good quality category, while two others Kim et al. and Martens et al. were classified as fair quality studies.

Studies with single-center observational designs showed slightly lower quality ratings ("Fair"), mainly due to smaller sample sizes (n = 201–206), the absence of *a priori* sample size justification, and limitations in controlling potential confounding factors [19,23]. Specifically, Kim et al. did not perform multivariable

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adjustment despite baseline differences in blood pressure, body mass index, and left ventricular ejection fraction between dose groups, while Martens et al. relied on paired antecedent–incident comparisons without formal adjustment for time-varying confounders. These limitations may have introduced residual confounding and affected the precision of the estimated dose–outcome associations. Although some included studies were assessed as fair quality, the direction of their findings remained broadly consistent with those of the good-quality studies. Consequently, despite the methodological limitations of these studies, their inclusion does not appear to substantially alter the overall interpretation of the available evidence.

Table 2. Quality Assessment of Included Studies Using the NIH Quality Assessment Tool for Cohort Studies

No	Author (Year)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	Quality (Score)
1	Kim et al., 2021 [19]	Y	Y	NR	Y	No	Y	Y	Y	Y	Y	Y	No	Y	No	Fair (10)
2	Rung et al., 2025 [20]	Y	Y	NR	Y	No	Y	Y	Y	Y	Y	Y	No	Y	Y	Good (11)
3	Dini et al., 2022 [21]	Y	Y	NR	Y	No	Y	Y	Y	Y	Y	Y	No	Y	Y	Good (11)
4	Kido et al., 2021 [22]	Y	Y	NR	Y	No	Y	Y	Y	Y	Y	Y	No	Y	Y	Good (11)
5	Martens et al., 2018 [23]	Y	Y	NR	Y	No	Y	Y	Y	Y	Y	Y	No	Y	No	Fair (10)
6	Chan et al., 2025 [24]	Y	Y	NR	Y	No	Y	Y	Y	Y	Y	Y	No	Y	Y	Good (11)
7	Doi et al., 2025 [25]	Y	Y	NR	Y	No	Y	Y	Y	Y	Y	Y	No	Y	Y	Good (11)

Characteristics of included studies

Table 3. Characteristics Studies

Author	Country	Study Design	Sample Size (n)	Male, n (%)	Age (mean±SD, years)	Functional Class (NYHA, %)	LVEF (mean±SD, %)	Follow-up
Kim et al., 2021 [19]	South Korea	Prospective cohort study	206	145 (70.4%)	63 ± 14	II: 89.8%; III: 10.2%	26.4 ± 6.1	Median 285 days (9.5 months)
Rung et al., 2025 [20]	USA	Retrospective cohort study	2,977	2,047 (68.8%)	67 (median, IQR 58–77)	Not reported	Not directly reported (claims-based proxy; 65% reduced EF)	≥3 months (median 14.5 months)
Dini et al., 2022 [21]	Italy	Prospective cohort study	727	615 (84.6%)	64 ± 11.8	>Class II: 32%	29.8 ± 6.2	Median 12.3 months
Kido et al., 2021 [22]	USA	Retrospective cohort study	721	499 (69.2%)	65.23 ± 12.70	Not reported	26.25 ± 8.59	1.82 ± 0.77 years (21.8 months)
Martens et al., 2018 [23]	Belgium	Retrospective cohort study	201	164 (81.6%)	67.7 ± 10.7	II: 67.8%; III: 30.7%; IV: 1.5%	29 ± 8	221 ± 114 days (7.3 months)
Chan et al., 2025 [24]	Taiwan	Retrospective cohort study	1,987	1,518 (76.4%)	Not reported (age-group based)	I–II: 66.4%; III–IV: 33.6%	28.1 ± 6.3	952 ± 383 days (31.7 months)
Doi et al., 2025 [25]	Japan	Retrospective cohort study	995	704 (70.8%)	69.6 ± 14.5	I: 15.0%; II: 48.3%; III: 28.3%; IV: 7.1%	39.1 ± 14.9	403 ± 170 days (13.3 months)

A total of 7,814 patients from six countries (Belgium, the United States, Italy, Taiwan, South Korea, and Japan) were analyzed across these seven observational studies. The majority of the patients evaluated were elderly, with a mean patient age of 63–69.6 years. Regarding gender distribution, there was a strong predominance of males, accounting for approximately 69.0% to 85.0% of the total study population. Where

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reported, patients in the included studies exhibited varying degrees of heart failure severity, ranging from NYHA class II to IV, while the LVEF ranged from 26.2% to 39.1%, consistent with HFrEF. Although all studies evaluated sacubitril/valsartan therapy, dose classification varied considerably, including comparisons between very low and standard doses, low, intermediate, and target doses, as well as dose categories based on daily dose achievement or target-dose attainment. Follow-up durations ranged from approximately 7 to 32 months. The detailed characteristics of the included studies are presented in Table 3.

Dose Classification Across Studies and Target Dose Attainment of Sacubitril/valsartan in Real-World Practice

A notable finding of this review was the heterogeneity in sacubitril/valsartan dose-classification strategies. Although all included studies assessed outcomes according to dose exposure, the criteria used to define dose categories varied considerably. Across the included studies, four main approaches to dose classification were identified. First, several studies, including Rung et al., Dini et al., and Martens et al., categorized patients according to the final achieved or maintenance dose during follow-up.

Table 4. Classification of Sacubitril/Valsartan Dose Categories Across Included Studies

Study	Target/High Dose Definition	Intermediate/ Moderate Dose Definition	Low Dose Definition	Method of Dose Classification
Kim et al., 2021 [19]	Not applicable	Standard-dose initiation (≥50 mg BID), n=100	Very-low-dose initiation (25 mg BID), n=106	Initial dose strategy (VLD vs. SD) and subsequent titration maintenance levels (25, 50, 100, 200 mg BID)
Rung et al., 2025 [20]	High dose: 97/103 mg BID (400 mg/day), n = 563	Medium dose: 49/51 mg BID (200 mg/day), n = 809	Low dose: 24/26 mg BID (100 mg/day), n = 1605	Terminal dose filled (final prescription fill in claims data)
Dini et al., 2022 [21]	Target dose: 97/103 mg BID (400 mg/day), n = 213	Intermediate dose: 49/51 mg BID (200 mg/day), n = 263	Low dose: 24/26 mg BID (100 mg/day), n = 251	Final maintenance dose achieved after titration
Kido et al., 2021 [22]	Target dose: 97/103 mg BID (400 mg/day), n = 205	Middle dose: 49/51 mg BID (200 mg/day), n = 165	Low dose: 24/26 mg BID (100 mg/day), n = 351	Most frequent dose filled during follow-up (claims data)
Martens et al., 2018 [23]	97/103 mg BID, n = 50	49/51 mg BID, n = 85	24/26 mg BID, n = 66	Final dose recorded at the last clinical assessment
Chan et al., 2025 [24]	Reach target dose: 200 mg BID, n = 162	Tolerability threshold: ≥50% target dose (≥200 mg/day), n = 871	Sub-target: <50% target dose (<200 mg/day), n = 905	Sustained dose level maintained during final 6 months
Doi et al., 2025 [25]	High dose: 400 mg/day, n = 397	Intermediate dose: 200–<400 mg/day, n = 239	Low dose: <200 mg/day, n = 359	Maximum dose achieved at least once during follow-up

Note: BID, twice daily; SD, standard dose; VLD, very low dose. Kim et al. classified patients according to the initial prescribed dose rather than target-dose attainment or achieved maintenance dose.

Second, Doi et al. classified patients based on the highest dose attained at any point during follow-up. Third, Kido et al. used the most frequently prescribed dose as a measure of long-term dose exposure. Finally, Chan et al. and Kim et al. adopted a tolerability-based approach, focusing on target-dose attainment, sustained dose achievement, or very-low-dose initiation strategies. These differences reflect the diverse methods used to evaluate dose exposure in real-world clinical practice. Differences in dose definitions across studies may influence synthesis results, as the dose categories used do not always reflect equivalent levels of sacubitril/valsartan exposure. Consequently, the reported outcomes likely reflect a combination of dosage levels, treatment tolerability, titration success, and the ability to maintain therapy throughout the follow-up period [23,26,27]. To facilitate interpretation, the original dose definitions used in each study are summarized in Table 4.

Studies evaluated dose trajectories using up-titration and follow-up dose assessments, because dose escalation was influenced by treatment tolerability and clinical characteristics [19–21,23,24]. However, many patients remain below this dose in routine clinical practice because of variations in titration patterns and treatment tolerability [28]. Although many patients remain on subtarget doses because of variable titration patterns in routine clinical practice, evidence indicates that even partial uptitration may result in clinically meaningful improvements, including enhanced cardiac function and reverse ventricular remodeling [29].

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Approximately 30% of patients achieve the target dose, whereas most continue receiving subtarget doses during follow-up [30,31].

The guideline-recommended target dose of sacubitril/valsartan is 97/103 mg twice daily [4,5]. Most Target-dose attainment of sacubitril/valsartan remains suboptimal despite its established clinical benefits. One of the reasons why many patients fail to achieve the target dose may be hypotension during dose titration [30]. The role of hypotension as a barrier to dose escalation is also reflected in several of the included studies. Doi et al. observed that patients who remained on low doses or failed to reach high doses experienced hypotension more frequently. Meanwhile, Rung et al. reported a higher frequency of hypotension in the group requiring dose reduction compared to the group where the dose was maintained or successfully increased. These findings indicate that tolerability issues can limit efforts to achieve more optimal dosages. Therefore, consideration of treatment tolerability is a crucial aspect alongside the evaluation of clinical outcomes. In a study conducted by Rung et al. (2025), it was found that patients who underwent down-titration or returned to their starting dose experienced higher rates of hypotension (30% vs. 14% and 12%) and acute kidney injury (36% vs. 17% and 15%), suggesting that treatment intolerance may limit dose escalation. This is supported by findings from the CHAMP-HF registry, where patients receiving lower doses of ARNI generally represented a more clinically vulnerable population, characterized by lower systolic blood pressure, progressive heart failure, and a higher prevalence of prior heart failure hospitalization and coronary artery disease, whereas renal function was broadly comparable across dose groups [32].

Dose of Sacubitril/valsartan and Hospitalization outcomes

The reported hospitalization outcomes differed across the included studies. While most studies evaluated HF hospitalization, one study focused on HF rehospitalization and another assessed a composite outcome comprising overall mortality and heart failure hospitalization. Overall, the included studies suggest that sacubitril/valsartan therapy was linked to favorable heart failure related hospitalization outcomes across different dose levels [21–25]. A similar trend has been reported in a recent real-world study, where higher average daily doses were associated with improved clinical outcomes before adjustment but not with heart failure hospitalization after propensity score weighting [33].

Although clinical benefits were observed even in patients receiving lower doses, most studies demonstrated greater reductions in HF hospitalization or composite outcomes following dose escalation. Notably, studies directly comparing intermediate and target doses found no significant additional reduction in HF hospitalization with target-dose therapy, indicating that much of the clinical benefit may already be achieved at intermediate doses [20]. Based on the findings of the REAL.IT study, no statistically significant difference in heart failure hospitalization rates was observed between the drug dosage groups. This phenomenon is thought to reflect the influence of variations in study design, dosage classification, and patient demographic characteristics [34]. From a clinical perspective, these results are highly logical because sacubitril/valsartan possesses the unique ability to simultaneously inhibit the neprilysin and renin-angiotensin-aldosterone systems. Through this dual mechanism, the drug is able to suppress the neurohormonal activation that damages the body, improve cardiac wall structure via reverse remodeling, and minimize the risk of hospital readmission for patients [35].

This favorable effect may extend beyond the index hospitalization. In a population of elderly patients with high comorbidity (mean Charlson index score of 3.1 to 3.5), the use of sacubitril/valsartan initiated during hospitalization for heart failure tended to result in lower rates of heart failure-related readmission and mortality compared to ACE inhibitors. However, these differences were not statistically significant at either the 3-month (aOR 0.696, 95% CI: 0.224–2.167) or 1-year (aOR 0.724, 95% CI: 0.325–1.612) follow-up periods [36]. Consistent with this observation, Kim et al. reported HF hospitalization rates were comparable between groups receiving very-low-dose (25 mg twice daily) and standard-dose (≥50 mg twice daily) sacubitril/valsartan (log-rank p=0.526), despite the very-low-dose group having lower baseline systolic blood pressure (102.8 vs. 118.7 mmHg; p<0.001) and LVEF (25.4% vs. 27.3%; p=0.026). These findings suggest that clinically meaningful benefits may still be achieved even with very-low-dose initiation in patients unable to tolerate standard doses [19].

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Table 5. Classification of Sacubitril/Valsartan Dose Categories Across Included Studies

Study	Hospitalization Parameter / endpoint Evaluated	Heart Failure Hospitalization	All-cause Hospitalization
Kim et al., 2021 [19]	Primary composite clinical outcome (Cardiovascular mortality + HF rehospitalization)	HF rehospitalization: No significant difference between VLD and SD (log-rank *p*=0.526).	NR
Rung et al., 2025 [20]	All-cause hospital admissions and Heart failure hospital admissions	HF hospitalization (IRR): • Low vs Medium: IRR 1.24 (p = 0.674) • Low vs High: IRR 1.70 (p = 0.223) • Medium vs High: IRR 1.37 (p = 0.509) • ANOVA across 3 groups: p = 0.26 (NS)	All-Cause Hospitalization (Estimated Ratio): • Low vs High: Ratio 2.66 (p < 0.001) • Low vs Medium: Ratio 1.52 (p < 0.001) • Medium vs High: Ratio 1.75 (p < 0.001)
Dini et al., 2022 [21]	Primary composite endpoint of all-cause mortality and HF-related hospitalization across 4 echo-defined hemodynamic profiles over 12.3 months.	Primary Composite Outcome (All-Cause Death + HFH): • Intermediate (49/51 mg BID) vs Low: HR 0.47 (p < 0.0001) • Target (97/103 mg BID) vs Low: HR 0.34 (p = 0.001)	NR
Kido et al., 2021 [22]	Co-primary outcomes of all-cause mortality and HF hospitalization	HF hospitalization (Propensity-Matched): • Low vs Target: HR 1.79 (p = 0.006) • Low vs Middle: HR 1.56 (p = 0.031) • Middle vs Target: HR 1.15 (p = 0.588, NS)	NR
Martens et al., 2018 [23]	Incident vs. antecedent HF hospitalizations	HF hospitalization: Overall incident vs antecedent: 23 vs 51 patients (p < 0.001) • 24/26 mg: p = 0.095, • 49/51 mg: p = 0.096, • 97/103 mg: p = 0.010 (significant)	NR
Chan et al., 2025 [24]	First unplanned HF hospitalization across age strata (<65, 65–74, ≥75 years) evaluating Tolerability (≥50% target dose) vs Discontinuation.	First Unplanned HF Hospitalization (Tolerability ≥50% Target vs Discontinuation): • Age <65: HR 0.41 (p < 0.001) • Age 65–74: HR 0.58 (p = 0.034) • Age ≥75: HR 0.60 (p = 0.029)	NR
Doi et al., 2025 [25]	First occurrence of HF hospitalization (standalone component) and primary composite outcome of all-cause death or HF hospitalization.	HF Hospitalization (Standalone Outcome): • High vs Low: HR 0.47 (p < 0.001) • High vs Intermediate: HR 0.68 (p = 0.09, NS)	Primary Composite Outcome (All-Cause Death + HFH): • High vs Low: HR 0.39 (p < 0.001) • High vs Intermediate: HR 0.64 (p = 0.03)

Note: NR = Not Reported; NS = Not Statistically Significant; VLD = Very Low Dose (25 mg BID); SD = Standard Dose (≥50 mg BID); HR = Hazard Ratio; IRR = Incidence Rate Ratio; HF = Heart Failure; HFH = Heart Failure Hospitalization; CV = Cardiovascular; ARR = Absolute Risk Reduction.

Dose of Sacubitril/valsartan and Mortality outcomes

Our findings indicate that both cardiovascular and all-cause mortality were lower in patients receiving sacubitril/valsartan at the target dose compared to those receiving lower doses. The findings are presented in Table 5. Doi et al. (2025) demonstrated that high-dose treatment (400 mg/day) reduced all-cause mortality by 75% (HR 0.25, p<0.001) and cardiovascular mortality by 77% (HR 0.23, p<0.001) when compared to low-dose groups. Similarly, Kido et al. (2021) found that patients maintained on the lowest dose (24/26 mg) faced a 2.56-fold higher mortality risk compared to those who achieved target dose (97/103 mg). These results confirm that achieving either the intermediate or target dose provides vastly superior survival protection for patients with HFrEF. Dini et al. (2022) reported that patients who successfully achieved the full target dose experienced a 66% reduction in the risk of adverse clinical outcomes specifically death or hospitalization. This clinical benefit was consistently observed regardless of the patients' baseline hemodynamic status. Meanwhile, regarding the non-elderly population (under 75 years of age), Chan et al. (2025) demonstrated that achieving at least half of the target dose significantly improved survival prospects. The reduction in mortality risk reached 70% in

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patients aged <65 years (HR 0.30) and 49% in those aged 65–74 years (HR 0.51). These findings suggest that securing a tolerable and sustainable dose provides substantial survival benefits, even when the full target dose is not achieved.

Table 6. Summary of Mortality Outcomes

Study	Mortality Parameter / Endpoint	Heart Failure / CV Mortality Outcome	All-Cause Mortality Outcome
Kim et al., 2021 [19]	Primary composite endpoint (CV mortality + HF rehospitalization)	No significant difference between VLD (25 mg BID) and standard dose (≥50 mg BID) (4 CV deaths total; log-rank p = 0.403).	NR
Rung et al., 2025 [20]	End-of-follow-up censoring mark (Administrative claims data; not evaluated as a primary hazard ratio endpoint)	NR	NR
Dini et al., 2022 [21]	Primary composite endpoint (All-cause death + HF hospitalization)	NR	Significant reduction in primary composite endpoint (Death + HFH): • Intermediate vs Low: HR 0.47 (p < 0.0001) • Target vs Low: HR 0.34 (p = 0.001)
Kido et al., 2021 [22]	Co-primary outcome (All-cause mortality analyzed as standalone endpoint)	NR	Significant mortality reduction in higher dose tiers: • Low vs Target: HR 2.56 (p < 0.001) • Low vs Middle: HR 1.67 (p = 0.024) • Middle vs Target: HR 1.54 (p = 0.166, NS)
Martens et al., 2018 [23]	Composite endpoint & Secondary outcome (All-cause mortality + HF admission)	4 CV deaths total (Accounting for 66% of overall 6 deaths).	6 total deaths (3.0%) over 221 days; ARR of 8.4% for composite death/HFH (p = 0.007).
Chan et al., 2025 [24]	Secondary endpoints (CV mortality and All-cause mortality analyzed separately across age strata)	Tolerability (≥50% target dose) vs Discontinuation: • Age <65: HR 0.41 (p = 0.009) • Age 65–74: HR 0.46 (p = 0.061, NS) • Age ≥75: HR 0.98 (p = 0.963, NS)	Tolerability (≥50% target dose) vs Discontinuation: • Age <65: HR 0.30 (p < 0.001) • Age 65–74: HR 0.51 (p = 0.044) • Age ≥75: HR 0.85 (p = 0.563, NS)
Doi et al., 2025 [25]	Secondary endpoints (CV mortality and All-cause mortality analyzed separately across dose tiers)	Significant reduction in high dose vs low dose: • High vs Low: HR 0.23 (p < 0.001) • High vs Intermediate: HR 0.64 (p = 0.28, NS)	Significant reduction in high dose vs low dose: • High vs Low: HR 0.25 (p < 0.001) • High vs Intermediate: HR 0.61 (p = 0.14, NS)

Note: NR = Not Reported; NS = Not Statistically Significant; VLD = Very Low Dose (25 mg BID); SD = Standard Dose (≥50 mg BID); HR = Hazard Ratio; CV = Cardiovascular; HF = Heart Failure; HFH = Heart Failure Hospitalization; ARR = Absolute Risk Reduction.

As stated in the 2022 AHA/ACC/HFSA Guideline, titration of guideline-directed medical therapy (GDMT) to target dose is recommended to reduce cardiovascular mortality and HF hospitalizations, provided the medication is well-tolerated. To maximize these benefits, the guidelines emphasize that uptitration and optimization should be pursued without delay, with titration every 1–2 weeks, adjusted based on the patient's symptoms, hemodynamic status, and laboratory findings [37]. Evidence regarding cardiovascular mortality was limited but generally favored sacubitril/valsartan therapy. Martens et al. reported that cardiovascular causes accounted for 66% of all deaths during follow-up, and initiating sacubitril/valsartan therapy was

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associated with an absolute risk reduction/ARR of 8.4% compared with the pre-treatment period. Similarly, Kim et al. showed no significant difference in cardiovascular mortality between patients initiated on a very-low dose (25 mg twice daily) and those receiving a standard starting dose, despite the poorer baseline clinical profile of the very low dose group. These findings suggest that even low dose initiation may provide clinically meaningful cardiovascular benefits while allowing subsequent dose optimization in patients unable to receive the standard dose due to tolerability limitations. Similar outcomes were observed among patients unable to tolerate full-dose therapy, where reduced-dose sacubitril/valsartan was associated with comparable risks of all-cause mortality (OR 1.67, 95% CI 0.26–10.82; p=0.63) and HF hospitalization (OR 0.79, 95% CI 0.08–8.08; p=1.00) relative to target-dose treatment [38].

Synthesis of Hospitalization Findings

Evidence across all seven studies demonstrates that sacubitril/valsartan dose escalation consistently reduces heart failure hospitalization (HFH) risks. The most pronounced reduction occurs when advancing patients from low (<200 mg/day) to intermediate doses (200–<400 mg/day or ≥50% target dose) [21,22,24,25]. Notably, studies comparing intermediate versus full target doses (400 mg/day) observed no statistically significant difference in HFH reduction [22,25]. Discrepancies emerged in an insurance claims study by Rung et al. (2025), which noted significant reductions in all-cause but not HF-specific admissions. Meanwhile, Martens et al. (2018) confirmed rapid readmission reductions early post-initiation, and Kim et al. (2021) showed that initiating a very low dose (25 mg BID) in vulnerable patients yielded readmission rates comparable to standard dosing. Collectively, these findings indicate that achieving a stable intermediate dose confers adequate protection against hospitalization.

Synthesis of Mortality Findings

Synthesized findings across the included studies confirm that achieving higher sacubitril/valsartan doses correlates directly with reduced all-cause and cardiovascular mortality [21–25]. Reaching an intermediate dose tier (≥50% target dose) or full target dose significantly lowers mortality risk compared to low-dose therapy [21,22,24,25]. Mirroring hospitalization trends, survival analyses revealed no significant difference in death risk between intermediate and full target dose groups [22,25]. However, mortality reduction is influenced by age, as survival benefits are prominent in non-elderly patients but diminished in individuals aged ≥75 years due to non-cardiovascular comorbidities [24]. In high-risk populations with baseline hypotension, initiating a very low dose (25 mg BID) maintained survival outcomes comparable to standard dosing [19]. Consequently, while low-dose therapy still provides meaningful protection compared to treatment cessation, clinicians should avoid clinical inertia settling for low initiation doses when dose escalation is tolerable since achieving a stable intermediate dose optimizes overall survival prognosis.

Table 7. Synthesis of Key Findings Across Included Studies

Pattern Identified	Supporting Studies
Higher doses associated with lower hospitalization	[21–23,25]
Higher doses associated with lower mortality	[21,24,25]
Intermediate doses may provide clinically meaningful benefit	[21,22,24]
Very-low-dose initiation may be feasible in selected patients	[19]
Treatment continuity may be important even without dose escalation	[20]
Baseline tolerability influences dose achievement	[19,20,24,25]

Biomarker Response During Sacubitril/Valsartan Dose Titration

In terms of pharmacokinetics, doubling the sacubitril/valsartan dose results in a proportional increase in plasma AUC for sacubitrilat (1.9-fold) and valsartan (1.7-fold) [39]. Furthermore, titration of sacubitril/valsartan from 100 mg to 200 mg twice daily in patients with HFrEF was associated with enhanced activation of the natriuretic system, evidenced by an increase in plasma cGMP (ratio of 1.38 vs. 1.24 at baseline) and elevated urinary cGMP and ANP levels. Concurrently, the dose increase was accompanied by reductions in biomarkers associated with heart failure severity and neurohormonal activation, including plasma NT-proBNP (ratios of 0.53 at day 7 and 0.56 at day 21), aldosterone (ratio of 0.79), and endothelin-1 (ratio of 0.80). These findings indicate that increasing the sacubitril/valsartan dose is associated with stronger activation of the natriuretic system and an improved neurohormonal profile in patients with HFrEF [40].

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Practical Clinical Implications, Titration Strategies, and Safety Monitoring in HFrEF

From a clinical perspective, the findings of this review highlight the importance of individualized dose optimization during sacubitril/valsartan therapy. Although higher dose categories were generally associated with more favorable outcomes, the included studies suggest that treatment success should not be assessed solely by achievement of the guideline-recommended target dose [20,24]. Chan et al. showed that achieving at least 50% of the target dose was associated with improved outcomes, while Dini et al. reported clinical benefits across multiple dose categories. Similarly, Rung et al. observed that most patients maintained stable doses throughout therapy, with no significant differences in heart failure-specific hospitalization rates across dose groups. Collectively, these findings support a patient-centered titration strategy that prioritizes attainment of the highest tolerated dose rather than rigid pursuit of target doses in all patients [20,21,24].

Contemporary heart failure guidelines emphasize that while achieving target doses is recommended, maintaining the highest tolerated dose and avoiding permanent drug discontinuation are paramount for long-term prognostic protection [4,37]. Real-world evidence from the included studies strongly supports this guideline-directed strategy through actionable approaches for patients unable to reach full target doses. First, for vulnerable patients or those with low baseline systolic blood pressure, initiating therapy with a very low dose (25 mg twice daily) provides a feasible gateway to build gradual tolerability without compromising treatment continuity [19]. Second, sustaining patients at an intermediate dose level (≥50% of the target dose) yields significant reductions in mortality and heart failure hospitalizations, offering clinical benefits comparable to full target doses [21,22,24,25]. Third, when adverse events occur, observational data and guidelines favor temporary down-titration over abrupt cessation, followed by active re-uptitration attempts once hemodynamic stability is restored [19,20,23].

Across the included real-world studies, hypotension and renal function decline emerged as the primary adverse events driving dose reduction and treatment discontinuation during sacubitril/valsartan titration [23–25]. Specifically, Rung et al. (2025) reported substantially higher rates of acute kidney injury (36%) and hypotension (30%) among patients requiring dose reduction compared to those maintaining stable doses, underscoring blood pressure and renal function as critical physiological boundaries in clinical practice. To manage these tolerability barriers, current guidelines advise routine surveillance of blood pressure, serum creatinine, eGFR, and potassium within 1–2 weeks post-initiation or dose adjustment [37,41,42]. When adverse events occur, guidelines recommend modifying reversible factors such as adjusting loop diuretics or non-essential vasodilators and prioritizing temporary down-titration over abrupt drug cessation [41,42]. Practically, structured monitoring acts not as a barrier to dose escalation, but as a clinical safety net that preserves treatment continuity and enables safe re-uptitration once physiological stability is restored [19,25,28].

Limitation

Despite generally consistent findings across the included studies, several limitations of the available evidence warrant consideration. First, a key methodological consideration in interpreting these findings is the observational nature of all included studies. In routine clinical practice, dose allocation and titration are influenced by baseline patient characteristics and treatment tolerability, creating the potential for confounding by indication [19,21,24]. Patients who achieve higher sacubitril/valsartan doses often have more favorable clinical profiles, including higher systolic blood pressure, better renal function, and lower comorbidity burden [19,24]. Consequently, part of the observed reduction in hospitalization and mortality risk may reflect underlying patient characteristics rather than medication dose alone. Kido et al. (2021) attempted to address this issue through propensity score matching, Doi et al. (2025) through time-updated Cox proportional hazards modeling, and Chan et al. (2025) and Dini et al. (2022) through multivariable adjustment; however, residual confounding cannot be completely excluded.

Second, the generalizability of the findings may be limited by the demographic characteristics of the included populations. Across studies, participants were predominantly male and older adults, reflecting the typical clinical profile of patients with HFrEF treated with sacubitril/valsartan in routine practice. Consequently, the applicability of these findings to women, younger patients, and other underrepresented patient populations remains uncertain [19–25].

Third, a quantitative meta-analysis was not performed because of substantial heterogeneity across the included studies. Differences in dose classification schemes (e.g., peak achieved dose vs. maintenance dose), outcome definitions, follow-up duration, and analytical approaches limited the comparability of effect estimates, making a structured narrative synthesis more appropriate. Finally, the potential for publication bias

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cannot be entirely ruled out, as studies reporting statistically significant positive dose-response outcomes are more likely to be published than those with null or equivocal results, and the literature search was restricted to published peer-reviewed studies in English and Indonesian.

Conclusions and Future Directions

Across different dose-classification systems, patients receiving higher dose categories generally exhibited more favorable clinical outcomes than those remaining on lower dose strata. In conclusion, the synthesis of evidence from these seven observational studies indicates a consistent dose-dependent association between sacubitril/valsartan dosing and clinical outcomes, where achieving target doses or at least an intermediate threshold (≥50% of target) is associated with lower all-cause and cardiovascular mortality as well as reduced heart failure hospitalizations. While real-world data indicate that many patients remain on lower doses due to clinical inertia or baseline physiological fragility, higher-dose maintenance was associated with lower mortality rates and reduced hospital admissions compared to low-dose regimens. Initializing therapy with a very low starting dose (25 mg twice daily) appeared well-tolerated in high-risk patients prone to treatment intolerance, supporting treatment continuity while achieving comparable clinical outcomes to standard initiation strategies.

Given the observational nature of the current evidence and the inherent potential for confounding by indication, further research is needed to clarify the optimal use of sacubitril/valsartan dose titration in clinical practice. Specifically, future studies should prioritize: (1) randomized controlled trials comparing distinct uptitration protocols (e.g., rapid versus gradual titration strategies) to determine optimal escalation trajectories; (2) dedicated evaluations targeting underrepresented populations, particularly female patients, younger cohorts, and individuals with complex comorbidities; (3) biomarker-driven research to identify predictors of dose tolerability and therapeutic response; and (4) implementation studies designed to mitigate systemic healthcare barriers and clinical inertia in routine practice.

Conflict of Interest

The authors report no financial, professional, or personal relationships that could be perceived as influencing the results or conclusions of this study.

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